

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/03955 A1

(51) International Patent Classification⁷: **A61K 9/00, 9/16**

(21) International Application Number: **PCT/IB01/01243**

(22) International Filing Date: **9 July 2001 (09.07.2001)**

(25) Filing Language: **Italian**

(26) Publication Language: **English**

(30) Priority Data:
MI2000A001548 10 July 2000 (10.07.2000) IT

(71) Applicant (for all designated States except US): **F.T. HOLDING S.A. [LU/LU]; 207, route d'Arlon, L-1150 Luxembourg (LU).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ROVERSI, Francesco [IT/CH]; Via S. Franscini, 40, CH-6900 Lugano (CH). CILURZO, Francesco [IT/IT]; Viale Pasubio, 6, I-20154 Milano (IT).**

(74) Agent: **GERVASI, Gemma; Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milano (IT).**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/03955 A1

(54) Title: **FAST RELEASE BIOADHESIVE MICROSPHERES FOR THE SUBLINGUAL ADMINISTRATION OF PROXIMATE PRINCIPLES**

(57) Abstract: Bioadhesive microspheres containing proximate principles dispersed in a polymeric matrix are suitable for the sublingual administration of the same.

FAST RELEASE BIOADHESIVE MICROSPHERES FOR THE SUBLINGUAL ADMINISTRATION OF PROXIMATE PRINCIPLES

FIELD OF THE INVENTION

The present invention refers to fast release bioadhesive microspheres for the sublingual administration of proximate principles, processes for the preparation of the same and pharmaceutical formulations including said microspheres.

STATE OF THE ART

The sublingual administration of proximate principles, i.e. by the absorption of these through the mucous of the sublingual area, presents considerable advantages compared to oral administration. In particular, since the drugs are absorbed very quickly and are not subjected to pre-systemic elimination, sublingual administration is particularly suitable in cases in which a rapid onset of the therapeutic action is desired or for drugs subjected to wide hepatic metabolism.

The main difficulty met in the sublingual administration of proximate principles is the short time these remain at the site of absorption, because of the continuous production and deglutition of saliva. If, in fact, the medicine dissolves slowly or is unable to penetrate the sublingual mucous, it is quickly removed before significant absorption takes place.

The strategy adopted until now in order to obviate this problem has been to increase the staying times of the medicine at the sublingual mucous. Bioadhesive formulations have in fact been recently developed, namely tablets and gels, made up of a bioadhesive matrix able to adhere to the mucous of the sublingual cavity and disintegrate slowly, thus maintaining the medicine in situ for a sufficient time period to obtain adequate absorption. These formulations are nevertheless characterized by a slow release of the proximate principle and are therefore unsuitable should one wish to obtain a rapid onset of the therapeutic action.

Therefore the need is felt to develop new formulations equipped with bioadhesive characteristics and which allow a ready release and hence rapid sublingual absorption, also of poorly hydrosoluble drugs.

SUMMARY OF THE INVENTION

A new fast release formulation for the sublingual administration of proximate

principles has now been surprisingly found. The inventors have in fact found that when a proximate principle is dispersed in non-crystalline form in a microparticle system made up of a bioadhesive polymer in microsphere form, with a mean diameter of less than 50 μ and preferably less than 30 μ , its dissolution speed is greater than that observed when the same proximate principle is in pure form. The aforesaid microspheres also show excellent adhesive capacities to the mucous. They therefore find particular utility in the sublingual administration of proximate principles, also poorly hydrosoluble ones.

DETAILED DESCRIPTION OF THE INVENTION

The present invention refers to fast release bioadhesive microspheres for sublingual administration of at least one proximate principle characterized in that they have a mean diameter of less than 50 μ and preferably less than 30 μ and contains said proximate principle dispersed in non-crystalline form in a bioadhesive polymer micromatrix of a molecular weight suitable for obtaining a fast release. The polymer is dispersed in the matrix in non-crystalline form.

The term "dispersed in non-crystalline form" means dispersed in such a way that it is not possible to identify the crystalline structure of the proximate principle by means of conventional techniques, namely D.S.C. and X-ray diffraction.

The microspheres of the present invention preferably contain at least one proximate principle in an amount usually of between 5 and 80%, preferably between 15 and 50% and a bioadhesive polymer in an amount of between 20 and 95%, preferably between 35 and 85%.

The microspheres of the invention can contain any proximate principle. For instance, the microspheres can contain hormones, vitamins, drugs that act on the cardiovascular and respiratory system, antimigraine, anaesthetics, myorelaxants, antihistamines, analgesics, antiinflammatories, antipyretics, hypnotic sedatives, stimulants of the nervous system, antiepileptic, antiparkinson, anticoagulants, hormonal antagonists, antimicrobial, antibiotics, peptide type drugs and vaccines. They are particularly suitable for the administration of poorly hydrosoluble proximate principles, of which increasing their solubility is desirable.

According to a particularly preferred application the proximate principle is selected from the group including oxicam, dihydropyridines, benzodiazepines, steroids,

alkaloids. Among these piroxicam, nifedipine, clonazepam and clobetasole, and morphine are particularly preferred.

According to a preferred application the bioadhesive polymer has a molecular weight suitable for obtaining a fast release and is selected from the group including derivatives of cellulose, starches, gums, scleroglucans, chitosans, vinyl, ethylene and acrylic polymers and copolymers and their derivatives. Particularly preferred among these are the derivatives of cellulose such as, for example, hydroxypropylmethylcellulose at different degrees of substitution characterized by a viscosity of a 2% solution in water of less than 4000 cp, among which for instance Methocel E5[®], Methocel E50[®] and Methocel F50[®], polyvinylpyrrolidone having a molecular weight of less than 1000000 Da.

Another group of polymers particularly preferred are the sodium or potassium salts of acidic acrylic polymers with a molecular weight of between 100000 and 1,000,000 Da.

In fact, the Applicant has found that only the acidic acrylic polymers in salified form with alkaline metals are able to impart mucoadhesiveness to the microspheres subject of the invention.

The acidic acrylic polymers usable to prepare the aforesaid salts are preferably selected from the group consisting of:

- a) copolymers of methacrylic acid and methyl methacrylate;
- b) copolymers of methacrylic acid and ethyl methacrylate,
- c) terpolymers of methacrylic acid, methyl methacrylate and methyl acrylate;

The particularly preferred acidic acrylic polymers belonging to class (a) are those commercially available under the EUDRAGIT[®] trademark and particularly the Eudragit S-100, with a mean molecular weight of around 135,000, and in which the free carboxylic groups and ester groups ratio is around 1:2; and the Eudragit L-100 with identical molecular weight and in which the aforesaid free carboxylic groups : ester groups ratio is around 1: 1.

The preferred acidic acrylic polymers belonging to class (b) are still the Eudragit and particularly the Eudragit L-100-55 with a mean molecular weight of 250000 Da and in which the ratio between free carboxylic groups : ester groups is around 1: 1. Preferred acidic acrylic polymers belonging to class (c) are still the Eudragit and

particularly the EUDRAGIT FS 30D, consisting of an aqueous dispersion of the terpolymer at 30% in weight, that contains only 10 to 12% of units of methacrylic acid.

The sodium and potassium salts of the acidic acrylic polymers usable in the microspheres subject of the invention are preferably prepared with a process that includes the following steps:

- i) a 5% solution in weight of the acidic acrylic polymer is prepared to which sodium or potassium carbonate is added in an amount able to impart neutrality to the aqueous solution;
- 10 ii) the solution obtained in the previous stage is dried by nebulization with the spray drying technique.

Optionally, the microspheres of the present invention also contain pharmaceutically acceptable excipients such as, for instance, wetting and solubilizing agents and diluents in amounts preferably between 2 and 20%. The solubilizing agents are preferably surfactants, among which are particularly 15 preferred polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodium lauryl sulphate.

The present invention also refers to processes for the production of the aforesaid microspheres. The microspheres of the invention can be produced through 20 processes usually used in the art such as, for example, coprecipitation, emulsion formation and evaporation of the solvent, spray congealing and spray drying, using conditions that lead to the attainment of the proximate principle dispersed in non-crystalline form. Particularly preferred for the production of the microspheres of the invention are spray drying techniques. In detail, the preparation of the 25 microspheres of the invention, according to these techniques, envisages the following stages:

- A) the proximate principle is dissolved in a solution or suspension of the bioadhesive polymer; and
- B) the resulting mixture is nebulized through the standard nozzle of a nebulizer at 30 a flow speed of between 5 and 60 ml/min and at an incoming air temperature of between 50° and 130°C.

The aforesaid solution or suspension contains a concentration of one of the

aforesaid polymers of between 0.5 and 20% p/v. Solvents that can be used for the preparation of said solution or suspension are, for instance, water, ethanol, isopropanol, methylene chloride, butanol, cyclohexane, hexane, acetone or mixtures of these.

- 5 The aforesaid proximate principle is added to said solution or suspension of the polymer in such an amount as to obtain a concentration of between 0.1 and 20% p/v.

Optionally, the polymer solution or suspension also contains one or more of the aforesaid pharmaceutically acceptable excipients at concentrations of between 0.5 and 20% p/v and preferably between 1 and 10% p/v.

- 10 The microspheres of the present invention present considerable advantages compared to the conventional formulations used sublingually. In fact, at the same time, they allow close contact between the proximate principle and the mucous and a high release speed, also for poorly hydrosoluble drugs, thus increasing the bioavailability and onset speed of the action of the proximate principle.

- 15 The microspheres of the present invention can be used as such, in the form of powders, or used for the preparation of pharmaceutical forms suitable for sublingual administration such as, for instance, tablets, capsules and sprays. Therefore, an additional aim of the present invention are pharmaceutical formulations for sublingual administration of proximate principles including the aforesaid microspheres usually together with pharmaceutically acceptable excipients. Among these are particularly preferred are formulations suitable for the administration of said microspheres in dispensers for mono or multidose powders.

- 20 The invention will now be illustrated in detail by the following examples, to be considered as illustrative and non-limiting, of the invention.

EXAMPLE 1

Preparation of nifedipine microspheres

- 30 Four solutions in methylene chloride/ethanol were prepared (90/10 v/v) having the following formulations:

1. Nifedipine 0.44% p/v, Methocel E5® 2.5% p/v
2. Nifedipine 0.44% p/v, Methocel E50® 2.5% p/v

3. Nifedipine 0.44% p/v, Methocel F50® 2.5% p/v

4. Nifedipine 0.44% p/v, Methocel E50® 2.5% p/v, Tween 80 0.13% p/v

The solutions were then nebulized through the standard nozzle (1mm internal diameter) of an SD04 nebulizer (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow speed of 20 ml/min, maintaining an incoming air temperature of 60°C and an outgoing air temperature of 40°C.

The microspheres obtained had a mean diameter of 20 μ , determined by the light scattering method, and a proximate principle content of more than 98% of the theoretical content.

In addition, the microspheres were analyzed using scanning calorimetry using a DSC 2010 apparatus (TA Instruments, United States), with a heating range from 30° to 225°C, scanning speed of 10°C/min and under continuous flow of nitrogen. The thermogram obtained shows the absence of thermal events in the temperature range considered and particularly at the melting temperature of nifedipine, at 173°C.

EXAMPLE 2

Determination of the dissolution speed of nifedipine microspheres

The dissolution speed of the various nifedipine microspheres prepared in Example 1 was assessed, compared with the dissolution speed of the pure nifedipine in micronized form with the paddle mixer method, described in the F. U. X. In detail, 33.3 mg of microspheres or 5 mg of pure nifedipine were put in a container thermostatically set at 37°C \pm 0.5°C in 500 ml of buffer solution at pH 7.4 containing 0.01% of sodium lauryl sulphate and kept under agitation at a speed of 100 rpm. The amount of nifedipine in the solution was continuously determined spectrophotometrically at a wavelength of 235 nm. The following table shows the mean of the results obtained from three determinations, expressed as a percentage of proximate principle dissolved at different time ranges:

Time(min utes)	Nifedipine	Microspheres Formul. 1	Microspheres Formul. 2	Microspheres Formul. 3	Microspheres Formul. 4
5	6.01	10.18	15.91	16.68	22.45
10	10.3	20.58	31.07	25.53	35.4
20	21.06	35.87	49.84	39.98	55.12
30	30.22	44.43	62.11	51.38	69.91
40	39.06	56.66	71.49	63.76	82.21
50	46.73	67.91	78.61	73.99	90.12
60	53.81	76.09	84.33	81.71	98.44

The results obtained show that all the prepared microspheres are characterized by a nifedipine dissolution speed which is greater than that of the pure substance. In addition, the introduction of a surfactant into the formulation further increases the release speed of nifedipine from the microspheres.

EXAMPLE 3

Preparation of piroxicam microspheres

Two solutions were prepared in methylene chloride-ethanol (90: 10 v/v), having the following formulation:

1. Piroxicam 2.5%, Methocel E5 @ 2.5%
2. Piroxicam 2.5%, polyvinylpyrrolidone having a molecular weight of 30000 Da, 2.5%.

The solutions were then nebulized through the standard nozzle (1mm internal diameter) of an SD04 nebulizer (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow speed of 20ml/min maintaining an incoming air temperature of 60°C and at an outgoing air temperature of 40°C.

The microspheres obtained had a mean diameter of 20 μ determined using the light scattering method, and a proximate principle content of more than 98% of the theoretical content.

The microspheres were also analyzed by scanning calorimetry using a DSC 2010 apparatus (TA Instruments, United States), with a heating range from 30° to 225°C, scanning speed of 10°C/min and under continuous flow of nitrogen. The thermogram obtained shows the absence of thermal events in the temperature

range considered and particularly at the melting temperature of piroxicam, at 203°C.

EXAMPLE 4

Determination of the dissolution speed of piroxicam microspheres

- 5 The dissolution speed of the various piroxicam microspheres prepared in Example 3 was assessed, compared with the dissolution speed of the pure piroxicam in micronized form, with the paddle mixer method, described in the F. U. X. In detail, 10 mg of the microspheres or 5 mg of pure piroxicam were placed in a container thermostatically set at 37°C±0.5°C containing 900 ml of distilled water kept under
10 agitation at a speed of 100 rpm. The amount of piroxicam in the solution was continuously determined spectrophotometrically at a wavelength of 354 nm. The following table contains the mean of the results obtained from three determinations, expressed as a percentage of proximate principle dissolved at different time ranges:

Time (minutes)	Piroxicam	Microspheres Formulation 1	Microspheres Formulation 2
5	3.59	8.35	18.74
10	4.21	15.92	34.79
15	4.96	23.09	43.80
20	5.97	27.91	47.69
25	6.92	31.10	49.84
30	7.93	33.98	50.69

15

As can be seen in the table, both microspheres are characterized by a piroxicam dissolution speed which is greater than that of pure piroxicam.

EXAMPLE 5

Preparation of clonazepam microspheres

- 20 A solution in methylene chloride-ethanol (90:10 v/v) was prepared containing 0.44% p/v of clonazepam and 2.5% of Methocel E5®. The solution was then nebulized through the standard nozzle (1mm internal diameter) of an SD04 nebulizer (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow speed of 20ml/min maintaining an incoming air temperature of 60°C and at an outgoing air

temperature of 40°C.

The microspheres thus obtained had a mean diameter of 20 μ , determined by the light scattering method, and a proximate principle content of more than 98% of the theoretical content.

- 5 The microspheres were also analyzed through scanning calorimetry using a DSC 2010 apparatus (TA Instruments, United States), with a heating range from 30° to 225°C, scanning speed of 10°C/min and under continuous flow of nitrogen. The thermogram obtained shows the absence of thermal events in the temperature range considered and particularly at the melting temperature of clonazepam.

10 EXAMPLE 6

Determination of the dissolution speed of clonazepam microspheres

- The dissolution speed of the clonazepam microspheres prepared in Example 5 was assessed, compared with the dissolution speed of the pure clonazepam in micronized form, with the paddle mixer method, described in the F. U. X. In detail, 15 60 mg of microspheres or 9 mg of pure clonazepam were placed in a container thermostatically set at 37°C \pm 0.5°C in 900 ml of distilled water containing 0.15% sodium lauryl sulphate and kept under agitation at a speed of 100 rpm. The amount of clonazepam in the solution was continuously determined spectrophotometrically at a wavelength of 252 nm. The following table shows the 20 mean of the results obtained from three determinations, expressed as a percentage of proximate principle dissolved at different time ranges:

Time (minutes)	Clonazepam	Microspheres
5	19.45	63.51
10	33.32	91.12
15	41.19	95.91
20	46.39	97.36
25	49.82	96.87
30	52.73	98.32

EXAMPLE 7**Preparation of clobetasol propionate microspheres**

A solution in methylene chloride-ethanol (90:10 v/v) was prepared containing 0.44% p/v of clobetasol and 2.5% of Methocel E50®. The solution was then nebulized through the standard nozzle (1mm internal diameter) of an SD04 nebulizer (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow speed of 20ml/min, maintaining an incoming air temperature of 60°C and at an outgoing temperature of 40°C.

The microspheres obtained had a mean diameter of 20µ, determined by the light scattering method, and they had a proximate principle content of more than 98% of the theoretical content.

The microspheres were also analyzed using X-ray diffraction. The results obtained from this analysis have shown that the proximate principle in the microspheres is non-crystalline.

EXAMPLE 8**Determination of the dissolution speed of clobetasol propionate microspheres.**

The dissolution speed of the clobetasol microspheres prepared in Example 7 was assessed, compared with the dissolution speed of the pure clobetasol in micronized form, with the paddle mixer method described in the F. U. X. In detail, 48 mg of microspheres or 7.2 mg of pure clobetasol were placed in a container thermostatically set at 37°C±0.5°C in 500 ml of distilled water containing 0.5% Tween 80 and kept under agitation at a speed of 100 rpm.

The amount of clobetasol in the solution was continuously determined spectrophotometrically at a wavelength of 252 nm.

The following table shows the mean of the results obtained from three determinations, expressed as a percentage of proximate principle dissolved at different time ranges:

Time (minutes)	Clobetasol	Microspheres
5	5.84	30.83
10	16.74	52.31
15	23.60	68.22
20	29.84	78.72
25	32.78	89.40
30	37.92	94.82

Preparation of the alkaline salts of the methacrylic copolymers

Stage i) Neutralization of the polyacrylic acids with sodium hydroxide and potassium hydroxide.

- 5 A 5% solution (5g/100ml) of the polyacrylic acid is prepared to which the stoichiometric amount of the alkaline hydroxide is added.

The following tables show the amounts of sodium and potassium hydroxide necessary to neutralize the EUDRAGIT L-100, S-100, L100-55, FS-30.

EXAMPLE	EUDRAGIT	NaOH (g)
8	L-100	1.070-1.178
9	S-100	0.645-0.715
10	L100-55	1.070-1.178

EXAMPLE	EUDRAGIT	KOH (g)
11	L-100	1.500-1.650
12	S-100	0.900 -1.000
13	L100-55	1.500-1.650

10

The sodium or potassium salt of the neutralized methacrylic copolymer is obtained by nebulizing the aqueous solution obtained in the previous stage (i) in a spray-dryer (SD04, Lab-Plant LTD, West Yorkshire, UK) using the following conditions.
Spray-dryer conditions:

Nozzle	0.75 mm
Incoming T	130°C
Outgoing T	60°C
Pump flow	10 ml/min
Air flow	44m ³ /h

The mucoadhesion tests are detailed as follows with the sodium and potassium salts respectively of the EUDRAGIT L-100, S-100, L 100-55,

TENSILE TESTS TO SEPARATION

5 INSTRUMENT USED: dynamometer with a 50 daN load cell

METHOD: mucin tablets of approx. 150 mg are prepared, with a diameter of 11.28mm, with the hydraulic press at a pressure of 10 tons for 30 sec.

The polymer tablets are prepared using the same method.

10 The mucin tablet is fixed to a steel plate and hydrated for 5 min. with 2 drops of water.

The polymer tablet is attached on the upper punch (12 mm diameter) and brought into contact with the mucin tablet for 5 min; the force needed to separate the two tablets is recorded.

POLYMERS ANALYZED:

15 ·Carbopol 934 (positive comparison)

·Eudragit L100 Na⁺ salt

·Eudragit L100 K⁺ salt

·Eudragit S100 Na⁺ salt

·Eudragit S100 K⁺ salt

20 ·Eudragit L100-55 Na⁺ salt

·Eudragit L100-55 K⁺ salt

The results of the experiments are shown in the following table

	Eudragit						
	Carbopo J 934	L100 Na	L100 K	L100-55 Na	L100-55 K	S100 Na	S100 K
Force of separation (N)	3.81	5.81	5.01	3.70	4.14	4.73	4.64
Detachment energy (J)	$3.66 \cdot 10^{-3}$	$4.29 \cdot 10^{-3}$	$4.01 \cdot 10^{-3}$	$3.18 \cdot 10^{-3}$	$4.44 \cdot 10^{-3}$	$3.46 \cdot 10^{-3}$	$4.77 \cdot 10^{-3}$

IN VIVO MUCOADHESION TESTS

Description:

- 5 A tablet is applied to the gum, of six healthy volunteers, and its staying time is assessed.

Tablets used:

Tablets obtained with an alternative press with a 6 mm diameter flat punch are used.

- 10 Each tablet weighs 25 mg.

The results are shown in the following table

		Volunteer					
		1	2	3	4	5	6
S100	Na	2h 10'	2h 30'	2h 30'	1h 55'	1h 40'	43'
	K	1h 45'	2h 35'	1h 35'	1h 20'	2h 15'	1h 00'
L100	Na	1h 30'	1h 25'	1h 20'	40'	1h 3'	45'
	K	1h 10'	1h 35'	1h 10'	40'	1h 5'	55'
L100-55	Na	1h 25'	50'	45'	45'	55'	30'

The tablets prepared with the unmodified polymers did not show any gum adherence capacity.

- 15 EXAMPLE 14- Morphine microspheres

The microspheres loaded with 30% of morphine were obtained by nebulizing through a standard nozzle (1mm internal diameter) of a spray-dryer (SD04, Lab-

Plant LTD, West Yorkshire, UK) a solution of H₂O: EtOH (80:20) containing a methacrylic polymer neutralized with NaOH or KOH and the proximate principle. The formulations for nebulization are shown in the following table.

Formulation	Morphine	Eudragit L100	Eudragit L100-55	Eudragit S 100	KOH	NaOH
1	0.85	2	-	-	0.66	-
2	0.85	-	2	-	0.66	-
3	0.85	-	-	2	0.47	-
4	0.85	2	-	-	-	0.40
5	0.85	-	2	-	-	0.40
6	0.85	-	-	2	-	0.28

5

Drying conditions:

Flow speed: 10 ml/min

Incoming air temperature: 90°C

Outgoing air temperature: 40°C

- 10 A sample of microspheres was analyzed with the technique of scanning calorimetry (DSC 2010, TA Instruments, USA). The morphine contained in all the microspheres proved completely amorphized or molecularly dispersed in the matrix.

- 15 The determination of the "in vitro" release was carried out with the paddle mixer method (FU X) on samples of microspheres containing morphine and on the micronized proximate principle.

Operative conditions:

- 20 temperature 37±0.5°C; rotation speed 100 rpm; dissolution medium: buffered physiological solution pH 7.4. The amount of morphine released from the microspheres was continuously determined spectrophotometrically, $\lambda = 285$ nm.

The results represent the mean of three determinations.

The dissolution profiles of the proximate principle and of the microspheres are shown in the following table.

Time	% morphine released						
	Micronized Morphine	Form. 1	Form. 2	Form. 3	Form. 4	Form. 5	Form. 6
5	32	95.56	94.85	96.45	98.71	99.12	96.15
10	61.2	97.25	95.69	97.91	99.19	99.73	97.21
15	82.2	98.98	96.86	98.68	99.58	99.99	97.98
20	91.1	99.58	97.45	99.19	99.73	100	98.49
25	95.6	99.98	98.18	99.78	100	100	99.08
30	98	100	99.56	100	100	100	99.37
35	99.7	100	99.86	100	100	100	99.39
40	100	100	100	100	100	100	100
45	100	100	100	100	100	100	100

The dissolution speed of the morphine is greater for all the prepared microspheres compared with the pure substance.

All the microspheres showed good bioadhesion properties.

5 Example 14- PIROXICAM MICROSPHERES

The microspheres loaded with 50% of piroxicam were obtained by nebulizing through a standard nozzle (1mm internal diameter) of a spray-dryer (SD04, Lab-Plant LTD, West Yorkshire, UK) a solution of H₂O: acetone (50:50) containing a methacrylic polymer neutralized with KOH and the proximate principle.

10 The composition of the fluid used for the nebulization is shown in the following table

Formulation	Piroxicam (g)	Eudragit L100 (g)	Eudragit L100-55 (g)	KOH (g)
1	2	2	-	0.66
2	2	-	2	0.66

Drying conditions:

Flow speed: 10 ml/min.

Incoming air temperature: 130°C

Outgoing air temperature: 60°C

A sample of microspheres was analyzed with the technique of scanning calorimetry (DSC 2010, TA Instruments, USA). The piroxicam contained in all the
5 microspheres proved completely amorphized or molecularly dispersed in the matrix.

The determination of the "in vitro" release was carried out with the paddle mixer method (FU X) on samples of microspheres containing morphine and on the micronized proximate principle.

10 Operative conditions:

temperature $37 \pm 0.5^\circ\text{C}$; rotation speed 100 rpm; dissolution medium: deionized water. The amount of piroxicam released from the microspheres was continuously determined spectrophotometrically at a wavelength of $\lambda = 354 \text{ nm}$. The results represent the mean of three determinations.

15 The dissolution profiles of the proximate principle and of the microspheres are shown in the following table.

Time	Micronized piroxicam	Formulation 1	Formulation 2
5	0.52	95.24	92.79
10	1.61	96.84	94.12
15	2.86	97.96	95.26
20	4.15	98.83	95.96
25	5.47	99.35	96.53
30	6.89	99.86	97.03
35	8.19	100	97.52
40	9.54	100	97.97
45	10.83	100	98.51
50	12.10	100	99.12
55	13.25	100	99.71
60	14.47	100	100

The dissolution speed of the piroxicam is greater for all the prepared microspheres compared with the pure substance.

- 5 All the microspheres showed good bioadhesion properties.

CLAIMS

1. Fast release bioadhesive microspheres for sublingual administration of at least one proximate principle, characterized in that they have a mean diameter of less than 50 μ and contain said proximate principle dispersed in non-crystalline form in
5 a micromatrix of bioadhesive polymer of molecular weight suitable for the attainment of a fast release.
2. Microspheres according to claim 1 characterized in that they have a mean diameter of less than 30 μ .
3. Microspheres according to claim 1 characterized in that they contain said
10 proximate principle in an amount of between 5 and 80% and said bioadhesive polymer in an amount of between 20 and 95%.
4. Microspheres according to claim 3 characterized in that they contain said proximate principle in an amount of between 15 and 50%.
5. Microspheres according to claim 3 characterized in that they contain said
15 bioadhesive polymer in an amount of between 35 and 85%.
6. Microspheres according to claim 1 characterized in that said proximate principle is a poorly hydrosoluble proximate principle.
7. Microspheres according to claim 1 characterized in that said proximate principle is selected from the group comprising hormones, vitamins, drugs that act on the
20 cardiovascular and respiratory system, antimigraine, anaesthetics, myorelaxants, antihistamines, analgesics, antiinflammatories, antipyretics, hypnotic sedatives, stimulants of the nervous system, antiepileptic, antiparkinson, anticoagulants, hormonal antagonists, antimicrobial, antibiotics, peptide type drugs and vaccines.
8. Microspheres according to claim 7 characterized in that said proximate principle
25 is selected from the group comprising oxicam, dihydropyridines, benzodiazepines, steroids, alkaloids.
9. Microspheres according to claim 8, characterized in that said proximate principle is selected from the group comprising piroxicam, nifedipine, clonazepam and clobetasol, and morphine.
- 30 10. Microspheres according to claim 1 characterized in that said bioadhesive polymer is selected from the group comprising derivatives of cellulose, starches, gums, scleroglucans, chitosans, vinyl, ethylene and acrylic polymers and

copolymers and their derivatives.

11. Microspheres according to claim 10 characterized in that said cellulose derivatives are hydroxypropylmethylcellulose at different degrees of substitution having a viscosity of a 2% solution in water of less than 4000 cp.

5 12. Microspheres according to claim 10 characterized in that said polyvinyl polymers are polyvinylpyrrolidones having a molecular weight of less than 1000000 Da.

13. Microspheres according to claim 10 characterized in that said acrylic polymers are sodium or potassium salts of acidic acrylic polymers with a molecular weight of
- 10 between 100000 and 1,000,000.

14. Microspheres according to claim 13, characterized in that said acidic acrylic polymers are selected in the group consisting of:

a) copolymers of methacrylic acid and methyl methacrylate;

b) copolymers of methacrylic acid and ethyl methacrylate,

15 c) terpolymers of methacrylic acid, methyl methacrylate and methyl acrylate.

15. Microspheres according to claim 14, in which said acidic acrylic polymers belonging to class (a), are selected in the group consisting of Eudragit S-100 and Eudragit L-100.

16. Microspheres according to claim 14, in which said acidic acrylic polymers
20 belonging to class (b), are the EUDRAGIT L100-55.

17. Microspheres according to claim 14, in which said acidic acrylic polymers belonging to class (c), are the Eudragit FS30D.

18. Microspheres according to claim 1 characterized in that they contain one or more pharmaceutically acceptable excipients.

25 19. Microspheres according to claim 18 characterized in that they contain said pharmaceutically acceptable excipients in an amount of between 2 and 20%.

20. Microspheres according to claim 18 characterized in that said pharmaceutically acceptable excipients are selected from the group comprising wetting and solubilizing agents and diluents.

30 21. Microspheres according to claim 20, characterized in that said solubilizing agents are surfactants.

22. Microspheres according to claim 21 characterized in that said surfactants are

selected from the group comprising polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodium lauryl sulphate.

23. Process for the preparation of microspheres according to claim 1 including the following stages:

5 A) the proximate principle is dissolved in a solution or suspension of the bioadhesive polymer; and

B) the resulting mixture is nebulized through the standard nozzle of a nebulizer at a flow speed of between 5 and 60 ml/min and at an incoming air temperature of between 50° and 130°C.

10 24. Process according to claim 23 characterized in that said solution or suspension of the polymer contains a polymer concentration of between 0.5 and 20% p/v.

25. Process according to claim 23 characterized in that said proximate principle is added to said solution or suspension of the polymer in such amount as to obtain a
15 concentration of between 0.1 and 20% p/v.

26. Process according to claim 23 characterized in that said solution or suspension of polymer contains one or more pharmaceutically acceptable excipients.

27. Process according to claim 26, characterized in that said solution or
20 suspension of polymer contains said excipients at a concentration of between 0.5 and 20% p/v.

28. Process according to claim 27 characterized in that said solution or suspension of polymer contains said excipients at a concentration of between 1 and 10% p/v.

25 29. Use of microspheres according to claim 1 for the preparation of pharmaceutical forms suitable for sublingual administration.

30. Pharmaceutical formulations for sublingual administration characterized in that they include microspheres according to claim 1.

31. Formulations according to claim 30, characterized in that they are suitable for
30 the administration of said microspheres in dispensers for mono or multidose powders.

32. Sodium and potassium salts of with a mean molecular weight of between

100000 and 1,000,000 selected from the group consisting of:

- a) copolymers of methacrylic acid and methyl methacrylate;
- b) copolymers of methacrylic acid and ethyl methacrylate,
- c) terpolymers of methacrylic acid, methyl methacrylate and methyl acrylate

5 33. Salts according to claim 33, in which said acidic acrylic polymers belonging to class (a), are selected between Eudragit S-100 and Eudragit L-100.

34. Salts according to claim 33, in which said acidic acrylic polymers belonging to class (b), are the EUDRAGIT L100-55.

35. Salts according to claim 33, in which said acidic acrylic polymers belonging to class (c), are the Eudragit FS30D.

36. Process to prepare the salts according to any one of the claims 33-36 including the following steps:

- i) a 5% solution in weight of the acidic acrylic polymer is prepared to which sodium or potassium carbonate is added in an amount able to impart neutrality to the aqueous solution;
- 15 ii) the solution obtained in the previous step is dried by nebulization with the spray drying technique.

INTERNATIONAL SEARCH REPORT

In..... Application No

PCT/IB 01/01243

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 452 268 A (WARNER LAMBERT CO) 16 October 1991 (1991-10-16) page 2, line 1 - line 6 page 2, line 29 - line 32 page 2, line 50 -page 3, line 22 page 3, line 39 - line 42; example 4 page 8, line 9 - line 18 page 9, line 1 -page 12, line 17; claims 1,2,5,9,11,15 --- -/-	1,2,18, 20,23, 24,26, 29-31



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

15 November 2001

Date of mailing of the international search report

29/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Marttin, E

INTERNATIONAL SEARCH REPORT

Application No

PCT/IB 01/01243

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30207 A (WATTS PETER JAMES ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 16 July 1998 (1998-07-16) page 5, line 8 - line 12 page 7, line 9 - line 14 page 8, line 1 - line 18 page 10, line 27 -page 11, line 2 page 11, line 25 -page 13, line 14; claims 1-5,11,15,16,19,20,22,29,35-40; examples 1-4,10,11	1,2,7, 10, 18-22, 29-31
X	WO 97 42255 A (BREITENBACH JOERG ;BASF AG (DE); KOLTER KARL (DE); SCHMITT ANGELIK) 13 November 1997 (1997-11-13)	32
A	page 1, line 6 - line 12 page 2, line 9 - line 11 page 2, line 30 - line 35 page 5, line 12 - line 21 page 6, line 21 - line 24 page 7, line 11 - line 16 page 10, line 24 -page 11, line 31; claims 1-4,6,9,12; examples 3,5,6	36
X	US 3 453 245 A (GLAVIS FRANK J) 1 July 1969 (1969-07-01)	32
A	the whole document	33-36
X	EP 0 857 475 A (BASF AG) 12 August 1998 (1998-08-12)	32,33
A	page 2, paragraph 1 page 2, line 32 -page 3, line 5 page 4, line 50 -page 5, line 9 page 5, line 22 - line 33; claims; examples 1,2	36
X	KIBBE A.H. (ED.): "HANDBOOK OF PHARMACEUTICAL EXCIPIENTS" 2000 , AMERICAN PHARMACEUTICAL ASSOCIATION AND PHARMACEUTICAL PRESS , WASHINGTON XP002182747 Polymethacrylates, page 401 - page 405. page 401, right-hand column, line 23 - line 42 page 403, left-hand column, line 2 page 403, left-hand column, last paragraph -right-hand column, paragraph 1	33,34
X	ANONYMOUS: "Specifications and test methods for Eudragit L100-55" July 1999 (1999-07) , RÖHM GMBH , DARMSTADT XP002182748 page 1, column 3, last paragraph -page 2, column 1, paragraph 2	32,34

	-/--	

INTERNATIONAL SEARCH REPORT

In Application No
PCT/IB 01/01243

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 16751 A (NYSTROEM CHRISTER ;PETTERSSON ANDERS (SE); HEDNER THOMAS (SE); LEN) 30 March 2000 (2000-03-30) page 3, line 9 -page 5, line 25 page 6, line 14 - last line; claims; examples 1,2	1-22, 29-31
A	US 5 202 159 A (CHEN LI J ET AL) 13 April 1993 (1993-04-13) column 3, line 12 - line 37 column 8, line 4 - line 19; claim 1	23-28
A	US 5 061 493 A (ROBERT SERGE ET AL) 29 October 1991 (1991-10-29) the whole document	1-22, 29-31
A	WO 91 16041 A (SMITH KLINE FRENCH LAB) 31 October 1991 (1991-10-31) page 1, line 8 - line 28 page 2, line 23 - line 30 page 4, line 1 - line 13 page 4, last line -page 5, line 3; claim 1	1-22
A	GUYOT M ET AL: "Nifedipine loaded-polymeric microspheres: Preparation and physical characteristics." INTERNATIONAL JOURNAL OF PHARMACEUTICS (AMSTERDAM), vol. 175, no. 1, 26 November 1998 (1998-11-26), pages 61-74, XP001041403 ISSN: 0378-5173 page 62, left-hand column, paragraph 3 page 64, left-hand column, paragraph 2 page 65, right-hand column, last paragraph -page 66, left-hand column, paragraph 1 page 73, right-hand column, paragraph 1	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

In application No

PCT/IB 01/01243

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0452268	A	16-10-1991	US 5077051 A	31-12-1991
			AU 4735593 A	25-11-1993
			AU 645791 B2	27-01-1994
			AU 7421291 A	17-10-1991
			CA 2040116 A1	11-10-1991
			EP 0452268 A2	16-10-1991
			IE 911185 A1	23-10-1991
			JP 4234811 A	24-08-1992
			PT 97304 A	31-01-1992
			ZA 9102724 A	29-01-1992
WO 9830207	A	16-07-1998	AU 725460 B2	12-10-2000
			AU 5568998 A	03-08-1998
			EP 0952822 A1	03-11-1999
			WO 9830207 A1	16-07-1998
			GB 2335357 A ,B	22-09-1999
			JP 2001508061 T	19-06-2001
			NO 993195 A	28-06-1999
WO 9742255	A	13-11-1997	DE 19617716 A1	06-11-1997
			AT 197808 T	15-12-2000
			AU 724502 B2	21-09-2000
			AU 2770097 A	26-11-1997
			BR 9708906 A	03-08-1999
			CN 1217733 A	26-05-1999
			DE 59702687 D1	04-01-2001
			WO 9742255 A1	13-11-1997
			EP 0896603 A1	17-02-1999
			ES 2153193 T3	16-02-2001
			HU 9903647 A2	28-03-2000
			JP 2000509422 T	25-07-2000
			NO 985094 A	03-11-1998
			US 6281282 B1	28-08-2001
			ZA 9703792 A	02-11-1998
US 3453245	A	01-07-1969	BE 681889 A	30-11-1966
			DK 113738 B	21-04-1969
			FR 90424 E	21-02-1968
			FR 1366002 A	10-11-1964
			FR 1481642 A	21-08-1967
			GB 1121965 A	31-07-1968
EP 0857475	A	12-08-1998	DE 19704293 A1	06-08-1998
			CN 1196232 A	21-10-1998
			EP 0857475 A2	12-08-1998
			JP 10218720 A	18-08-1998
			US 6080811 A	27-06-2000
WO 0016751	A	30-03-2000	AU 6492899 A	10-04-2000
			BR 9913948 A	12-06-2001
			EP 1115384 A1	18-07-2001
			NO 20011502 A	23-03-2001
			WO 0016751 A1	30-03-2000
US 5202159	A	13-04-1993	JP 4230625 A	19-08-1992
US 5061493	A	29-10-1991	FR 2621483 A1	14-04-1989
			AT 99940 T	15-01-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Publication No

PCT/IB 01/01243

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5061493	A	CA 1328610 A1	19-04-1994
		DE 3887066 D1	24-02-1994
		DE 3887066 T2	11-05-1994
		EP 0311540 A1	12-04-1989
		ES 2061713 T3	16-12-1994
		JP 1128928 A	22-05-1989
WO 9116041	A	31-10-1991	
		AT 131383 T	15-12-1995
		AU 649041 B2	12-05-1994
		AU 7748191 A	11-11-1991
		CA 2081109 A1	27-10-1991
		DE 69115476 D1	25-01-1996
		DE 69115476 T2	05-06-1996
		DK 526524 T3	29-01-1996
		EP 0526524 A1	10-02-1993
		ES 2080314 T3	01-02-1996
		WO 9116041 A1	31-10-1991
		GR 3019298 T3	30-06-1996
		IE 911381 A1	06-11-1991
		NZ 237930 A	26-08-1993
		PT 97476 A ,B	31-01-1992
		ZA 9103072 A	25-11-1992